## REMARKS

A check for the requisite fees for a three-month extension of time and for filing a Request for Continued Examination (RCE) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 17, 18, 65 and 66 are pending. Claims 1-15 and 19-64 are cancelled herein without prejudice or disclaimer. Claim 17 is amended herein by incorporating limitations of a dependent claim. Claims 65 and 66, which are added, find basis in the application as filed. For example, basis can be found at page 2, line 15. No new matter is added.

**REJECTION OF CLAIMS 1, 3, 4, 6-11, 13-15, 17-23, 25-38, 40-46 AND 48-64 UNDER 35 U.S.C. §112, SECOND PARAGRAPH**

Claims 1, 3, 4, 6-11, 13-15, 17-23, 25-38, 40-46 and 48-64 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. It respectfully is submitted that the grounds for this rejection are moot with respect to claims 1, 3, 4, 6-11, 13-15, 19-23, 25-38, 40-46 and 48-64 which are cancelled herein.

With respect to claims 17 and 18, which are rejected as improperly setting forth alternative language, the rejection also is moot. Claim 17 and dependent claim 18, as amended, do not recite alternative language.

**THE REJECTION OF CLAIMS 1, 3, 4, 6-11, 13-15, 17-23, 25-38, 40-46 AND 48-64 UNDER 35 U.S.C. §103(a)**

**Claims 1-13, 15-19, 22-26, 30, 31, 33-44 and 47-64**

Claims 1-13, 15-19, 22-26, 30, 31, 33-44 and 47-64 are rejected under 35 U.S.C. §103(a) as unpatentable over Leavitt *et al.* (WO 94/17405) in view of any of Johnson *et al.* (NEJM 293: 675, 1975), Meis *et al.*, (Am J Obstet Gynecol 187: S54, 2002) or Keirse (Br J Obstet Gynecol 97: 149, 1990) and further in view of Weiner *et al.* or Andersen *et al.* The Examiner states that, Leavitt *et al.* teaches the determination of biochemical markers of imminent or preterm delivery to aid in clinical decisions regarding the administration or treatments, and the remaining references allegedly teach that the treatment can be a progestational agent. The Examiner alleges that any of Johnson *et al.*, Meis *et al.* or Keirse teaches the efficacy of progesterone treatments in reducing preterm delivery and that Weiner

*et al.* or Andersen *et al.* teaches that treatment with tocolytic agents is not beneficial in patients with membrane rupture. The Examiner alleges that one of ordinary skill in the art would have tested a pregnant patient determined to have biochemical markers indicative of impending preterm delivery for the status of the fetal membranes and to treat those patients with intact fetal membranes indicated as at risk for having impending delivery with a pregnancy-prolonging agent because of the direct suggestion in Leavitt *et al.* to do so. The Examiner further alleges that it would have been obvious to treat a patient so identified with a known efficacious pregnancy-prolonging agent such as progesterone in light of the teachings of any of Johnson *et al.*, Meis *et al.* or Keirse. The Examiner also alleges that Applicant improperly traversed the rejection by attacking the references individually. This rejection is respectfully traversed.

As a preliminary matter, Applicant respectfully submits that, in responding to the rejections under 35 U.S.C. §103(a) in the previous responses, **Applicant did not attack the references individually**. Rather, Applicant, following the analytical framework of *Graham v. John Deere*, described the teachings of each reference and differences from the claimed subject matter, then demonstrated that the combination of the references does not result in the claimed subject matter. None of the references, singly nor in any combination, teaches or suggests selection of the particular combination of identifying subjects at risk for preterm delivery based on detection of fetal fibronecting for treatment with a progestational agent.

**Relevant law**

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

Further, that which is within the capabilities of one of ordinary skill in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980).

Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

**The rejected claims**

Claim 17 is directed to a method a method of screening and treating a subject by monitoring the level of fetal fibronectin in a body fluid sample from a subject, and, if the level is indicative of a risk for preterm or imminent delivery, administering 17-α-hydroxy-progesterone caproate. Claim 18 recites that the level of fetal fibronectin must be above a threshold level. Dependent claims 65 and 66 recite that the body fluid sample is vaginal fluid.

**Teachings of the cited art and differences from the claimed methods**

**Leavitt *et al.* (WO 94/17405)**

Leavitt *et al.* teaches assays that distinguish between subjects with impending immediate delivery having intact membranes, from those in whom the membranes have ruptured. Leavitt *et al.* teaches an assay that distinguishes those patients at risk for impending delivery with intact membranes from those at risk for impending delivery with ruptured membranes. The assays of Leavitt *et al.* require measurement of the level of two markers: a fetal restricted antigen, such as fetal fibronectin, and IGFBP-1. The combination of the two markers permit distinguishing between women at risk for preterm delivery who have intact membranes from those at risk who have ruptured membranes. Those who have intact membranes would be candidates for administration of tocolytic therapy (administration of β-mimetics or magnesium sulfate), the inhibit contractions. Progestational therapy, as established by the secondary references and the instant application is for administration to prevent preterm labor.

Leavitt *et al.* does not teach or suggest the particular combination of measuring the level of fetal fibronectin as the basis for identifying patients at risk for preterm delivery and, then administering, any agent that delays delivery. Leavitt *et al.* teaches measuring the levels of fetal fibronectin, and, then measuring the levels of IGFBP-1 to distinguish women with preterm labor who have ruptured membranes from those with intact membranes. Depending upon the levels of IGFBP-1 in women determined to be at risk for preterm delivery, tocolytic therapy (therapy with agents such as β-mimetics or magnesium sulfate) can be administered to stop the contractions. There is no point to administer these agents to women with ruptured membranes. Tocolytic therapy, which is therapy that inhibits the progress of labor, is different from progestational therapy, which is therapy that maintains pregnancy (see, the references of record). Progestational therapy is not tocolytic therapy, nor, as discussed below does any of the cited art suggest otherwise. Tocolytic therapy, as defined, for example, by Anderson *et al.* involves administration of agents that are β-mimetics or are magnesium sulfate. Weiner *et al.* indicates that progesterone was administered to women to prevent preterm labor; once preterm labor started tocolytic therapy (such as terbutaline or magnesium sulfate) was administered, clearly demonstrating a recognized distinction in the art. The tocolytic agents, which have undesirable side-effects and cannot be tolerated for extended periods, are administered once preterm labor begins. They are not administered prophylactics as the 17α-hydroxyproges-terone caproate can be.

The instant claims recite monitoring the level of fetal fibronectin in a body fluid sample from a subject, and, **if the level of fetal fibronectin** is indicative of a risk for preterm delivery, administering 17-α-hydroxyprogesterone caproate. Leavitt *et al.* teaches that if the levels of IGFBP-1 are indicative of intact membranes, administering **tocolytic** therapy to stop preterm delivery, not as a prophylactic to women at risk of preterm delivery. Leavitt *et al.* is essentially irrelevant to the instant claims.

Leavitt *et al.* fails to teach or suggest monitoring fetal fibronectin levels and administering any agent. Leavitt *et al.* teaches a method for determining whether a women with elevated fetal fibronectin has ruptured or intact membranes. Further, Leavitt *et al.* teaches administering tocolytic therapy, which prevents contractions once preterm labor has commenced, not prophylactic administration of progestational agents. The secondary references do not cure the deficiencies in the teachings of Leavitt *et al.*

**Johnson *et al.* (NEJM 293: 675, 1975)**

Johnson *et al.* does not cure the deficiencies in the teachings of Leavitt *et al.* Johnson *et al.* teaches a possible obstetric use of 17α-hydroxyprogesterone caproate in the prevention of premature labor, in patients with a history of spontaneous abortions. Johnson *et al.* does not teach or suggest measuring fetal fibronectin, to identify patients at risk for preterm delivery, for prophylactic treatment with17α-hydroxyprogesterone caproate.

**Meis (Am J Obstet Gynecol 187: S54, 2002)**

Meis teaches that small studies from the 1970s and 1980s suggested a benefit of 17α-hydroxyprogesterone therapy in preventing preterm birth, and a larger double-blind study was undertaken. Meis teaches that treatment with 17α-hydroxyprogesterone reduced the risk of **preterm birth in women with a documented history of preterm birth**. Meis, like Johnson *et al.*, relies on a patient history of **spontaneous preterm** delivery to identify subjects for administration of 17α-hydroxyprogesterone. Meis does not suggest use of fetal fibronectin levels to identify subjects to whom to administer 17α-hydroxyprogesterone. Hence Meis does not cure the deficiencies in the teachings of Leavitt *et al.* and Johnson *et al.*

**Keirse (Br J Obstet Gynecol 97: 149, 1990)**

Keirse teaches a meta-analysis of controlled trials of a variety of progestational agents and concludes that there is no support that 17α-hydroxyprogesterone caproate protects against miscarriage, but suggests that it does reduce the occurrence of preterm birth. Keirse teaches that 17α-hydroxyprogesterone caproate is the most fully studied progestational agent (page 149, col. 2, last full paragraph). Keirse teaches that its study indicates that injections of 17α-hydroxyprogesterone caproate may reduce the occurrence of preterm birth among women so-treated (page 153, col. 2, second full paragraph). Keirse does not teach or suggest measuring fetal fibronectin as a basis for identifying patients at risk for preterm delivery, for treatment with17α-hydroxyprogesterone caproate. Thus Keirse does not cure the deficiencies in the teachings of Leavitt *et al.*, Johnson *et al.* and Meis.

**Weiner *et al.* (Am J Obstet Gynecol 159: 216-222 (1988))**

Weiner *et al.* describes the result of a trial comparing bed rest with tocolysis using intravenous ritrodrine, terbutaline, or magnesium sulfate for **treatment of preterm labor after membrane rupture.** Weiner *et al.* is not concerned with nor directed to therapy that can prevent preterm labor, but rather therapy that is administered following its onset. Once

preterm labor has begun, there is no need to assess any markers associated with risk of preterm labor. Weiner *et al.* teaches that treatment of labor after preterm premature rupture of the membranes does not improve perinatal outcome after 28 weeks gestation (page 222, first paragraph).

Thus, Weiner *et al.* is virtually of no relevance to any of the instant claims. The instant claims are directed to methods and products for screening and treating women at risk of preterm delivery with progestational agents. Weiner *et al.* is concerned with women with ruptured membranes and the use of tocolytic agents, not progestational agents, for treatment of such subjects. Weiner *et al.* provides no teaching or suggestion regarding the identification of subjects at risk for preterm delivery by measuring a biochemical marker, nor of administering a progestational agent to subjects so identified. Thus Weiner *et al.* does not cure the deficiencies in the teachings Leavitt *et al.*, Johnson *et al.*, Meis and Keirse.

**Andersen *et al.***

Andersen *et al.* teaches that preterm labor is a major problem in obstetrics, and that about a third of preterm births are associated with preterm premature rupture of membranes (PROM) (page 336, col. 1, second full paragraph). Andersen *et al.* teaches that in some instances preterm labor follows PROM, while in other situations preterm delivery becomes medically indicated because of the development of infection or other pregnancy complications (*Id.*). Anderson *et al.* provides a discussion of various methods for assessing the onset of preterm delivery, and concludes that assessment is largely empirical. Significantly, Andersen *et al.* does not discuss testing the level of fetal fibronectin to assess risk, nor does Anderson *et al.* suggest any tests that would assess risk rather than detecting onset.

Anderson *et al.* indicates that there are two classes of tocolytic therapy beta-symphathomimetics, such as ritrodrine and terbutaline sulfate, and intravenous magnesium sulfate. Anderson *et al.* indicates the progesterone injections have been suggested to prevent preterm delivery, but that progesterone is ineffective in stopping established preterm labor. Anderson *et al.* also indicates that there is no data to show improvement in preterm delivery rate with progesterone therapy. Hence, Anderson *et al.* teaches that progesterone therapy is very different from the tocolytic agents that stop preterm labor, and that it is not proven to be effective. Thus Anderson *et al.* does not cure the deficiencies in the teachings Leavitt *et al.*, Johnson *et al.*, Meis, Keirse and Weiner *et al.*

**ANALYSIS**

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons and reasons of record.

**The combination of the teachings of Leavitt *et al.* and Johnson *et al.* or Meis or Keirse with the teachings of Weiner *et al.* or Andersen *et al.* does not result in the instantly claimed methods.**

As discussed above, the instant claims are directed to methods of screening and treating subjects identified to be a risk of preterm delivery and treating such subjects with 17α-hydroxyprogesterone caproate, which is administered to prolong labor and prevent the onset of preterm labor.

Leavitt *et al.* fails to teach or suggest a method in which fetal fibronectin level is assessed to identify women at risk of preterm delivery. As discussed above, Leavitt *et al.* is directed to a method in which the level of fetal fibronectin is assessed, and, if elevated, the level of IGFBP-1 is assessed to distinguish subjects with intact membranes from those with ruptured membranes. None of Meis, Keirse and Weiner *et al.* and/or Anderson *et al.* teaches or suggests identifying women at risk for preterm delivery by measuring fetal fibronectin. All treat subjects with prior history of preterm labor or spontaneous abortion. Thus, none cure the deficiencies in the teachings Leavitt *et al.* . Thus the combination of teachings of Leavitt *et al.* with any or all of the teachings of Meis, Keirse and Weiner *et al.* and/or Anderson *et al.* does not result in the instantly claimed methods.

Further, Leavitt *et al.* contemplates tocolytic therapy (i.e. therapy with beta-symphathomimetics, such as ritrodrine and terbutaline sulfate, or intravenous magnesium sulfate), which is designed to prevent contractions and cannot be administered for extended periods. Leavitt *et al.* does not suggest any agents that reasonably can be administered prophylactially to prolong pregnancy. None of Meis, Keirse and Weiner *et al.* and/or Anderson *et al.* teaches or suggests that the population of patients to whom progestational therapy is administered should be selected by assessing the level of fetal fibronectin, nor do these references, singly or in combination, teach or suggest a method for identifying women at risk for preterm delivery **before** symptoms are manifest. Therefore, the combination of teachings of the references does not result in the instantly claimed methods.

Leavitt *et al.* contemplates tocolytic therapy, and only after testing for a marker such as fetal fibronectin and then testing for **a second marker to rule** out those who have

ruptured membranes by measuring the levels of IGFBP-1. The purpose is to identify those women with ruptured membranes for whom treatment with a β-mimetic or magnesium sulfate is too late. None of Leavitt *et al.*, Meis, Keirse and Weiner *et al.* and/or Anderson *et al.* teaches or suggest elimination of the second step in the method of Leavitt *et al.* nor use of fetal fibronectin by itself to identify patients at risk of preterm delivery for treatment with 17α-hydroxy progesterone. Thus, the combination of teachings of these references cannot and does not result in the instantly claimed methods.

**Rebuttal to the Arguments of the Examiner**

**1. The Examiner sates that:**

> Leavitt *et al.* teach their determinations of biochemical markers of impending imminent preterm delivery and of fetal membrane status to aid clinical decisions regarding administration of treatments to prolong pregnancy in pregnant patients at 12 to 37 weeks gestation (see e. g. pages 4-6, 8). Applicant 's suggestion, ten years later, to test the same markers for the .same purpose as taught in the Leavitt et al. reference is not found unobvious for the reasons of record.

The Examiner has incorrectly read Leavitt *et al.* As discussed above, Leavitt *et al.* teaches a method for distinguishing whether a patient at risk for preterm delivery has ruptured membranes by testing **two** markers: a fetal restricted antigen, such as fetal fibronectin **and** IGFBP-1. The instant claims require testing of fetal fibronectin only. There is no suggestion in Leavitt *et al.* to eliminate the second step of its method.

**2. The Examiner continues** and states that progestational agents are known as among the tocolytic agents that function to prevent or reduce contractions prior to preterm labor (citing Andersen *et al.*, da Fonseca *et al.*), and not different therefrom. It respectfully is submitted that this is not a correct reading of either reference, nor is it a proper characterization of progesterone.

Anderson *et al.* teaches that there are "two classes of tocolytic therapy: beta-symphathomimetics, such as ritrodrine and terbutaline sulfate, and intravenous magnesium sulfate." Progestational agents, are not beta-symphathomimetics nor magnesium sulfate. Hence they are not tocolytics as defined by Anderson *et al.* nor any of the references of record.

da Fonesca *et al.* describes a study that evaluated the effects of prophylactic vaginal progesterone in decreasing preterm birth rate in a population of women who had one previous spontaneous birth. da Fonesca *et al.* teaches that progesterone blocks the oxytocin effect of

prostaglandin, and, is not beta-mimetic and certainly is not magnesium sulfate. In the study, women admitted for preterm labor, who had been treated with progesterone, were treated with β-mimetics (tocolytics). da Fonesca *et al.* concludes that progesterone is effective in preventing preterm delivery, but does not teach that it is a tocolytic agent. da Fonesca *et al.* teaches that progesterone exerts a direct effect on the uterus via its own cellular receptor so that the contractile capacity is maintained. Thus, neither Anderson *et al.* nor da Fonesca *et al.* nor any references teaches that progesterone is a tocolytic; rather it is a distinct agent that can be used to prevent preterm delivery, not stop it.

3). **The Examiner states** there are "no working examples showing pregnancy prolongation other than suggesting that which has been demonstrated in the art with progesterone (da Fonseca *et al.*)or 7α-hydroxyprogesterone (Johnson *et al.*, Yemini *et al.*, Keirse, or Meis *et al.*)or omega-3 fatty acid supplementation (Allen et al. or Olsen et al.)."

The Examiner is reminded that there is no requirement for working examples, nor has the Examiner provided any documentary or scientific evidence to doubt that progesterones prevent or lower the risk of preterm delivery or extend pregnancy. The art of record and specification establish the activity. The instant claims are directed to a method of screening and diagnosis in which subjects are tested to assess the level of fetal fibronectin. If the levels of fetal fibronectin are elevated, 7α-hydroxyprogesterone caproate is administered. None of the art of record teaches or suggests the claimed method. Leavitt *et al.* is directed to a method for identifying women with ruptured membranes; there is no suggestion in Leavitt *et al.* nor any secondary reference to modify its method, and then combine one step of it method with treatment with 7α-hydroxyprogesterone caproate.

The secondary references, to the extent any are relevant establish that 7α-hydroxyprogesterone caproate can be effective in prolonging pregnancy. All rely on histories of preterm labor or spontaneous abortions to select subjects for administration of a progesterone. None suggest an alternative population.

4. **The Examiner** urges that all obviousness rejections rely on hindsight, and that such is permissible:

> it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

> reconstruction is proper. See In ye McLaughlin, 443 F. 2d 1392, 170 USPQ 209 (CCPA 1971). Nothing in the combination of known markers of impending imminent preterm delivery and of fetal membrane status with known treatments for pregnancy prolongation is gleaned only from applicant's disclosure.

Applicant respectfully disagrees. None of the art of record teaches or suggests use of fetal fibronectin as a marker to select populations of women for treatment the 17α-hydroxyprogesteron caproate. As noted, Leavitt *et al.* teaches a method for distinguishing women in preterm labor with ruptured membranes from those whose membranes have not ruptured. The instant claims, are not directed to such methods, but employ fetal fibronectin as a marker to assess *risk* of preterm delivery for administration of progesterone, which prolongs pregnancy and can be administered for long periods. This is different from administration of tocolytics, such as terbutaline or magnesium sulfate that are administered after contractions have started, and that have very undesirable side-effects, limiting their administration.

**5) The Examiner urges that applicant is attacking the references individually.** This is not correct. The analytical framework relied on by the undersigned is a review of each reference and an identification of its deficiencies, followed by combining the references to then determine whether all limitations of the claims can be found in the combination of teachings. The undersigned has not argued the references separately. As demonstrated above, the combination of teachings of the references does not result in the method as claimed. None of the references, singly nor in combination, teaches measuring fetal fibronectin to identify patients at risk of preterm delivery, and none suggests or teaches that any marker indicative of risk should be employed to identify subjects for administration of a 17α-hydroxycaproate. Leavitt *et al.* teaches a method that requires two tests and is distinguishing women in preterm labor who have intact membranes from those who have ruptured membranes; and all other cited references assess risk of preterm delivery by prior history. Tocolytics, such as β-mimetics or magnesium sulfate would be administered to the subjects in Leavitt *et al.* determined to be in preterm labor with intact membranes. None would be candidates for administration of 17α-hydroxyprogesterone.

**Claims 1-13, 15, 17-44 and 47-64**

Claims 1-13, 15, 17-44 and 47-64 are rejected under 35 U.S.C. §103(a) as being obvious over Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in

view of Weiner *et al.* or Andersen *et al.* and further in view of Dullien (U.S. Pat. No. 5,480,776). Applicant respecftully traverses the rejection for the reasons of record and further for the reasons discussed above.

As discussed above, Leavitt *et al.* fails to teach or suggest use of fetal fibronectin to identify women at risk of preterm delivery. Leavitt *et al.* is directed to a method for distinguishing women who have ruptured membranes from those with intact membranes so that tocolytic therapy, with its undesirable side-effects, is not administered to subjects with ruptured membranes. None of the secondary references, Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.*, concern tocolytic therapy, which as described in references, such as Anderson *et al.* is treatment with a β-mimetic or magnesium sulfate, to stop uterine contractions, not prevent them. The secondary references that assess the effectiveness of progesterone as a prophylactic. None of these references, nor any reference of record suggests selecting women for treatment by assessing the level of fetal fibronectin.

Dullien, (U.S. Pat. No. 5,480,776), which teaches a method for detecting the onset of labor by measuring estriol concentration. Dullien does not cure the deficiencies in the teachings of Leavitt *et al.*, Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.*. Dullien *et al.* does not suggest testing fetal fibronectin nor any marker that would indicate risk of preterm delivery; Dullien assesses a marker that indicates the onset of preterm labor for which tocolytic agents, such as β-mimetics or magnesium sulfate, that stop labor. Dullien does not suggest identifying patients for treatment with 17-α-hydroxy progesterone. Thus, Dullien does not cure the deficiencies in the teachings of the cited references.

**Claims 7, 14, 17-19 and 22-26**

Claims 14, 45 and 46 are rejected under 35 U.S.C. §103(a) over Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.* and further in view of Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)) teachings of the role of n-3 fatty acids in prolonging gestation or Olsen *et al.* (Lancet 339: 1003 (1992)), cited teaching that omega-3 fatty acids can prolong pregnancy, reasons of record. Applicant respectfully traverses the rejection for reasons of record and for those reasons discussed above.

As discussed above, the combination of teachings of Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.* does

not result in the instantly claimed methods. Neither Allen *et al.* nor Olsen *et al.* cures the deficiencies in the teaches of Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.* Neither Allen *et al.* nor Olsen *et al.* teaches or suggests measuring levels of fetal fibronectin to identify subjects for treatment with agents, such as 17 α-hydroxyprogesterone caproate (or other such agents), to ameliorate the risk of preterm delivery. As discussed above, Leavitt *et al.* is directed to a method for identifying subjects in preterm labor with ruptured membranes from those with intact membranes for whom treatment with tocolytic therapy (therapy with agents defined by the art as β-mimetics and magnesium sulfate. The secondary references directed to treatment to prolonging therapy, either do not select patients for treatment, or rely on prior history of preterm delivery, for treatment with progestational agents. Therefore, the combination of teachings of the references does not result in the instantly claimed methods.

**Claims 7, 14, 17-25, 30-34, 45 and 46**

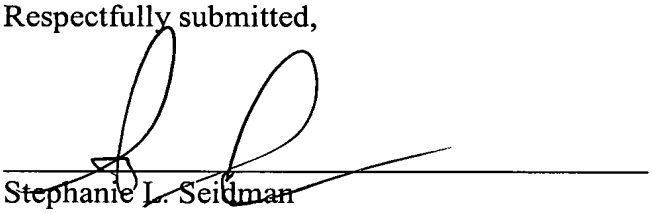
Claims 7, 14, 17-25, 30-34, 45 and 46 are rejected under 35 U.S.C. §103(a) over Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.*, further in view of Dullien *et al.* and further in view of Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)) or Olsen *et al.* (Lancet 339: 1003 (1992)). This rejection respectfully is traversed for the reasons of record and those discussed above.

As discussed above, neither the combination of teachings of Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.*, further in view of Dullien *et al.* nor the combination of teachings of Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.* and further in view of Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)) or Olsen *et al.* does not results in the instantly claimed methods. Thus, the combination of teachings of Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse, further in view of Weiner *et al.* or Andersen *et al.*, further in view of Dullien *et al.* and further in view of Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)) or Olsen *et al.* cannot result in the instantly claimed methods for the reasons discussed above and in the arguments of record.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,



Stephanie L. Seidman
Reg. No. 33,779

Attorney Docket No. 17101-025001 / 826
**Address all correspondence to**:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com